

June 14, 2002

James Cooper
Executive Director
Phenolic Benzotriazoles Association
1850 M Street, NW Suite 700
Washington, DC 20026

Dear Mr. Cooper:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for phenolic benzotriazoles category, posted on the ChemRTK HPV Challenge Program Web site on December 4, 2001. I commend the Phenolic Benzotriazoles Association for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its HPV Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Phenolic Benzotriazoles Association advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer

M. E. Weber

**EPA Comments on Chemical RTK HPV Challenge Submission:
Phenolic Benzotriazoles**

SUMMARY OF EPA COMMENTS

The sponsor, the Phenolic Benzotriazoles Association, submitted a test plan and robust summaries to EPA for the Phenolic Benzotriazoles category dated October 26, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 4, 2001.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter adequately supports the grouping of the category members with the information provided.
2. Physicochemical and Environmental Fate Data. The submitter needs to provide measured water solubility data for these chemicals. The submitter also needs to provide input data for its transport and distribution (fugacity) models.
3. Health Endpoints. The submitter has proposed conducting reproductive toxicity studies. However, adequate evaluation of reproductive organs from available repeated-dose studies and the availability of developmental toxicity studies may satisfy the reproductive/developmental toxicity endpoints. If this information on the reproductive endpoint is not available, EPA agrees with the submitter's test plan to conduct reproductive toxicity studies. In addition, the submitter needs to address several deficiencies in the robust summaries and inconsistencies in the test plan.
4. Ecotoxicity. The data for acute ecotoxicity are inadequate for fish, invertebrates and algae. EPA disagrees with the submitter that no further acute toxicity testing is necessary. Also, the log K_{ow} values (4.2–7.25) for these chemical suggest that the submitter needs to conduct chronic aquatic toxicity testing in daphnia.

EPA requests that the submitter advise the Agency within 60 days of any modifications to this submission.

**EPA COMMENTS ON THE PHENOLIC BENZOTRIAZOLES
CHALLENGE SUBMISSION**

Category Definition

The submitter has proposed a category covering four phenolic benzotriazoles: 2-(2'-hydroxy-5'-methylphenyl)benzotriazole (CAS No. 2440-22-4), 2-(2'-hydroxy-5'-octylphenyl)benzotriazole (CAS No. 3147-75-9), 2-(2'-hydroxy-3',5'-di-t-amylphenyl)benzotriazole (CAS No. 25973-55-1), and 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol (CAS No. 70321-86-7). These compounds contain a common benzotriazole functional group, plus a mono- or di-substituted phenol. The category definition is unambiguous.

Category Justification

The submitter's primary justification for the category is twofold: (1) the similarity of the structural backbone of all members (phenolic benzotriazoles), and (2) the similar or regular pattern of the chemical, physical, and toxicological properties of the members.

Physicochemical and Environmental Fate Data. The physicochemical and environmental fate properties of the category members follow the regular pattern suggested by their molecular weights. All category members are reported to be essentially nonvolatile and have low water solubilities. The available biodegradability data for these compounds indicate that they are “not readily biodegradable.”

Health Endpoints. The submitter concludes that similar toxicological properties of the category members include low acute toxicity, lack of genotoxicity, and moderate repeated-dose toxicity, with the liver and kidney as target organs. The submitter claims that the category members share “a common basis of action” because of toxicological similarities. However, supporting information on toxicokinetics for these chemicals was not provided.

Ecotoxicity. EPA agrees that these phenolic benzotriazoles are likely to follow expected patterns of acute and chronic aquatic toxicity.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The test plan for these endpoints, except as noted below, is adequate for the purposes of the HPV Challenge Program.

Water Solubility. The submitter reported measured water solubility ranges (e.g. < 1 mg/L) or estimated values for all four chemicals in the category. According to OECD Guideline 105, the water solubility for a chemical should be measured unless the value is $\leq 1 \mu\text{g/L}$. Estimated values and qualitative descriptions of solubility are thus not acceptable. Therefore, the submitter needs to provide accurate measured water solubility values for the four chemicals or test for water solubility using OECD guidelines.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The submitter’s approach to these endpoints is acceptable for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

EPA agrees with the submitter’s conclusion that all four phenolic benzotriazoles have been adequately tested for acute toxicity, repeated-dose toxicity, and genetic toxicity. However, the submitter needs to address certain reporting deficiencies. (See Specific Comments on robust summaries.)

Reproductive Toxicity. The test plan calls for reproductive toxicity testing (OECD Guideline 421) for 2-(2-hydroxy-5-methylphenyl)benzotriazole and 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol, the lowest and highest molecular weight compounds of the category, respectively. In accordance with HPV Challenge Program guidance, adequate evaluation of reproductive organs from available repeated-dose studies and the availability of developmental toxicity studies may satisfy the reproductive/developmental toxicity endpoints. The submitter needs to provide information on the evaluation of reproductive organs from the repeated-dose toxicity studies. If this information is not available, EPA agrees with the submitter’s test plan to conduct the reproductive toxicity studies in rats with appropriate route of administration on the two chemicals mentioned above.

Developmental Toxicity. Adequate studies for developmental toxicity (gavage) in rodents are available for two members of the category. EPA agrees that these data can be extrapolated to the remaining category members, provided the submitter demonstrates toxicokinetic similarities among the category members.

Ecological Effects (fish, invertebrate and algal toxicity)

EPA disagrees with the submitter that there is no need for further aquatic toxicity testing. Because ecotoxicity values for all members of the category were greater than their reported water solubilities (<1 mg/L) and were determined using unacceptable co-solvents that exceeded the maximum acceptable co-solvent concentration of 100 mg/L, EPA considers these data inadequate. The submitted test results may underestimate ecotoxicity because nominal concentrations of test chemical were used in some cases and/or because inappropriate and excessively high concentrations of solvent were used. In the case of 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol, the vehicle used was a surfactant that exceeded the maximum concentration of 100 mg/L. Surfactants should not be used as vehicles for most types of chemicals due to possible interference with the toxic action of the chemical being tested.

On the basis of physical and chemical properties, as well as structure-activity estimation techniques such as EPIWIN, acute toxic effects would be predicted for the least hydrophobic chemicals tested in addition to possible chronic effects. The observation of undissolved chemical in some of these tests should have led the submitter to consider an alternative approach for dissolving the test chemicals. In addition, the log K_{ow} values (4.2–7.25) for these chemicals suggest that the submitter needs to conduct chronic aquatic toxicity testing in daphnia.

If the submitter conducts further ecotoxicity testing, all tests should be carried out using flow-through test methods and mean measured concentrations. As for choice of test substances, the least hydrophobic chemical should be re-tested at or below its water solubility limit for acute toxicity in fish. If effects are observed, the submitter should proceed to acute toxicity testing on invertebrates and algae. If no effects are observed in the fish acute test, no further acute testing would be warranted. Nevertheless, EPA recommends a 21-day chronic reproductive study in daphnia (OECD 211). The more hydrophobic members of the category may also exhibit chronic toxicity in aquatic organisms at or below their water solubility limits. The submitter needs to determine which of these chemicals should be tested to determine the pattern of acute and chronic toxicity within the category. More precisely measured water solubility data can provide direction for further testing. In the robust summary for the fish acute test on 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol, the substantial chemical loss reported in the 96-hour exposure period may be due to rapid photolysis. If this is the case, any future acute testing in fish, daphnia or algae should be conducted according to the guidance on photolysis in the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD Series on Testing and Assessment - Number 23) available at the following website: <http://www.oecd.org/ehs/test/monos.htm>.

Specific Comments on the Robust Summaries

Environmental Fate.

Transport and Distribution (Fugacity)

The submitter's treatment of fugacity is adequate, except that the submitter needs to provide the assumption and data inputs to the model for all four chemicals (see Guidance for Robust Summary preparation).

Health Effects. None of the robust summaries list the purity of the test substance. For the test substance purity and the specific omissions outlined below, the submitter needs to indicate which data elements were not reported in the original study or add the available reported data to the robust summary.

Acute Toxicity. For 2-(2'-hydroxy-5'-octylphenyl)benzotriazole, the submitter needs to reconcile the inconsistencies between the administered doses "between 1.25 and 10 mg/kg" and the reported

LD₅₀=1000 mg/kg), and also with the LD₅₀ in the table on page 54 (LD₅₀>1000 mg/kg) and in Table 2, page 11 (LD₅₀>10,000 mg/kg).

For 2-(2'-hydroxy-3',5'-di-t-amylphenyl)benzotriazole, the submitter needs to reconcile the inconsistency in the study date between the robust summary (1978) and the chemical data summary table on page 82 (1993).

Repeated Dose Toxicity. For all robust summaries, the submitter needs to provide method details and to report frequency of data collection, statistical methods, specific hematology and clinical chemistry endpoints, and specific organs that were weighed and examined histologically. The submitter also needs to state the NOEL/NOAEL and LOAEL values in mg/kg-day (body weight basis).

2-(2'-Hydroxy-5'-methylphenyl)benzotriazole. For the 90-day dog study, the submitter needs to report results for the recovery animals. For the cancer bioassays in rats and mice, the submitter needs to state the NOAEL/LOAEL values for noncancer effects.

2-(2'-Hydroxy-3',5'-di-t-amylphenyl)benzotriazole. For the 90-day rat study, the submitter needs to cite the correct OECD Guideline: 408 (subchronic oral toxicity in rodents) rather than 409 (subchronic oral toxicity in non-rodents). For the 90-day dog study, the submitter needs to address the inconsistency in the NOEL of >15 mg/kg-day on page 100, but <15 mg/kg-day on page 101, in the chemical summary table on page 82, and in the category summary Table 2 of the Test Plan on page 11. The robust summary needs to specify clearly which dose levels produced elevated serum levels of bilirubin, GPT, GOT, and alkaline phosphatase.

Genetic Toxicity.

2-(2'-Hydroxy-5'-methylphenyl)benzotriazole. For the study on reverse mutation in bacteria, the submitter needs to add the number of replicate plates and the cytotoxic concentration; also, the submitter needs to reconcile the study date in the robust summary (1979) with that in the chemical summary table on page 17 (1982).

2-(2'-Hydroxy-3',5'-di-t-amylphenyl)benzotriazole and 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol. For the studies on reverse mutation in bacteria, the submitter needs to add the number of replicate plates and the cytotoxic concentration.

Developmental Toxicity. 2-(2'-Hydroxy-5'-methylphenyl)benzotriazole. For both studies, the submitter needs to add the group size and the endpoints that were examined at termination. For the study in rats, the submitter needs to correct the study duration ("0 days").

2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol. The submitter needs to add the group size and the specific endpoints that were examined at termination. In addition, since the study was conducted under GLP and OECD Guideline 414, the submitter needs to explain the assignment of a reliability code of 2b rather than 1.

Ecotoxicity. Chemicals were tested above their water solubility limits in most of the summarized studies. For test substance purity and other omissions outlined below, the submitter needs to indicate which data elements were not included in the original study or add the available data to the robust summary.

Fish. In the acute toxicity test for 2-(2'-hydroxy-5'-methylphenyl)benzotriazole, missing critical data elements include pH, hardness, dissolved oxygen, vehicle used, concentration, temperature, and test substance purity. In the acute toxicity test for 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol, there was no explanation in the robust summary for the substantial chemical loss

during the 96-hour exposure period, which may be due to photolysis. None of the remaining robust summaries for acute fish toxicity contained sufficient information on test substance purity or water chemistry parameters.

Invertebrates. The studies are inadequate because they were for 24 rather than 48 hours, as required by OECD and other widely accepted test guidelines.

Algae. None of the robust summaries contain sufficient information on test substance purity or water chemistry parameters. Two of the three robust summaries did not indicate the concentration of solubilizing vehicle used, while solvent content exceeded the maximum amount allowed in the third robust summary. In addition, the robust summary for the study on 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol was inadequate because details of test methods were not reported.

Follow-up Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to this submission.